PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAF/PG4978	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11648	International filing date *(day/month/year)* 20.10.2003	Priority date *(day/month/year)* 22.10.2002
International Patent Classification (IPC) or both national classification and IPC C07D319/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.04.2004	29.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Boletti-Cremers, K Telephone No. +49 89 2399-8541

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11648

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-4, 6-66	as originally filed
5	filed with telefax on 14.04.2004

Claims, Numbers

1-15	filed with telefax on 14.04.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 11

   because:

   ☒ the said international application, or the said claims Nos. 11 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10,12-15
	No:	Claims	

2. Citations and explanations

   see separate sheet

POINT I.

In view of the support pointed out by the Applicant for the amendments of the definitions of radicals R^{1a} and R^{2a} , those amendments are acceptable according to the requirements of Art 34 (2) (b) , last sentence PCT.

POINT III

For the assessment of the presently worded claim 11, on the question whether it is industrially applicable, no unified criteria exist in the PCT.
The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a new medical treatment.

POINT V.

The following document , quoted in the I.S.R., has been considered as relevant for the examination of the present application . Its numbering will be adhered to for the rest of the procedure.

(1) WO-A-98/29405.

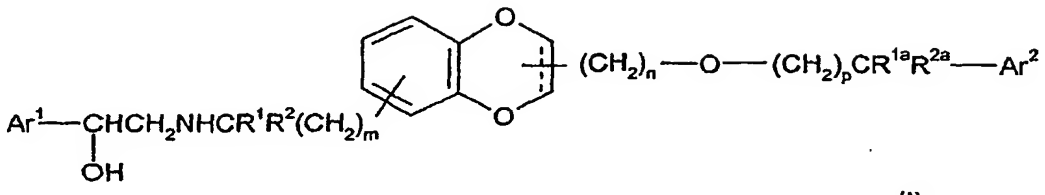
In view of the content of (1) both novelty and inventiveness of the claimed matter on file can be acknowledged , because the compounds on file are neither disclosed nor suggested in that document.

Formal point.

Claim 2 reads unclearly because it refers to preferred definitions under the wording "except that" , wihch could read as an exclusion more than a preferred embodiment.
The Applicant is invited to reformulate said claim at the entry of the application into the regional European proceedings.

CLAIMS

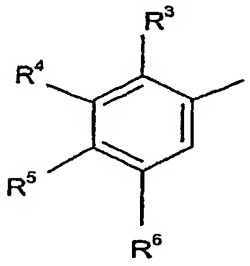
1. A compound of formual (I):



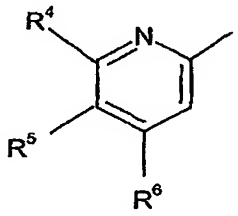
(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

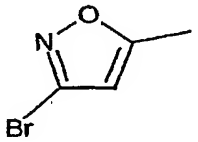
Ar^1 is a group selected from



(a)

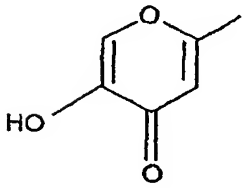


(b)



(c)

and



(d)

wherein R^4 represents hydrogen, halogen, $-(CH_2)_qOR^7$, $-NR^7C(O)R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-NR^7R^8$, $-OC(O)R^9$ or $OC(O)NR^7R^8$,

and R^3 represents hydrogen, halogen or C_{1-4} alkyl;

or R^4 represents $-NHR^{10}$ and R^3 and $-NHR^{10}$ together form a 5- or 6- membered heterocyclic ring;

R^5 represents hydrogen, halogen, $-OR^7$ or $-NR^7R^8$;

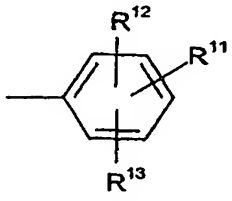
R^6 represents hydrogen, halogen, haloC_{1-4}alkyl, $-OR^7$, $-NR^7R^8$, $-OC(O)R^9$ or $OC(O)NR^7R^8$;

R^7 and R^8 each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^7R^8$, $-SO_2NR^7R^8$ and $-OC(O)NR^7R^8$, R^7 and R^8 independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

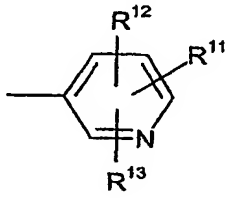
R^9 represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4;

Ar^2 is a group:



or



wherein

R^{11} is selected from hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6}haloalkyl, XCO_2R^{16}, $-XC(O)NR^{15}R^{16}$, $-XNR^{14}C(O)R^{15}$, $-XNR^{14}C(O)NR^{15}R^{16}$, $-XNR^{14}C(O)NC(O)NR^{15}R^{16}$, $-XNR^{14}SO_2R^{15}$, $-XSO_2NR^{17}R^{18}$, XSR^{14}, $XSOR^{14}$, XSO_2R^{14}, $-XNR^{15}R^{16}$, $-XNR^{14}C(O)OR^{15}$, or $XNR^{14}SO_2NR^{15}R^{16}$,
or R^{11} is selected from -X-aryl, -X-hetaryl, or -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, cyano, nitro, $CONR^{15}R^{16}$,

-$NR^{14}C(O)R^{15}$, SR^{14}, SOR^{14}, -SO_2R^{14}, -$SO_2NR^{17}R^{18}$, -CO_2R^{16}, -$NR^{15}R^{16}$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

X is $-(CH_2)_r-$ or C_{2-6} alkenylene;

r is an integer from 0 to 6, preferably 0 to 4;

R^{14} and R^{15} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)- and R^{14} and R^{15} are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, -NHC(O)(C_{1-6}alkyl), -SO_2(C_{1-6}alkyl), -SO_2(aryl), -CO_2H, and -CO_2(C_{1-4}alkyl), -NH_2, -NH(C_{1-6}alkyl), aryl(C_{1-6}alkyl)-, aryl(C_{2-6}alkenyl)-, aryl(C_{2-6}alkynyl)-, hetaryl(C_{1-6}alkyl)-, -$NHSO_2$aryl, -NH(hetarylC_{1-6}alkyl), -$NHSO_2$hetaryl, -$NHSO_2$(C_{1-6}alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

or R^{14} and R^{15}, together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered nitrogen – containing ring;

or where R^{11} is $-XNR^{14}C(O)NR^{15}R^{16}$, R^{14} and R^{15} may, together with the -NC(O)N- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an imidazolidine ring, such as imidazolidine-2,4-dione;

or where R^{11} is $-XNR^{14}C(O)OR^{15}$, R^{14} and R^{15} may, together with the -NC(O)O- portion of the group R^{11} to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an oxazolidine ring, such as oxazolidine-2,4-dione;

R^{16} is selected from hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl;

or where R^{11} is $-XC(O)NR^{15}R^{16}$ or $-XNR^{14}C(O)NR^{15}R^{16}$, R^{15} and R^{16} may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

R^{17} and R^{18} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)-, or R^{17} and R^{18}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

and R^{17} and R^{18} are each optionally substituted by one or two groups independently selected from halo, C_{1-6}alkyl, and C_{3-7}cycloalkyl, C_{1-6}haloalkyl;

R^{12} is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl;

R^{13} is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl;

R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^1 and R^2 is not more than 4;

one of R^{1a} and R^{2a} is selected from hydrogen and C_{1-4}alkyl, and the other of R^{1a} and R^{2a} represents hydrogen or C_{1-4}alkyl;

m is an integer of from 1 to 3;
n is an integer of from 1 to 4; and
p is zero or an integer of from 1 to 3;

and ⎯ represents a single or double bond.

2. A compound of formula (I) as defined in claim 1, or a salt, solvate or physiologically functional derivative thereof, except that:
R^{1a} and R^{2a} each represent hydrogen;
and in the group Ar^1, either:
R^4 represents halogen, $-(CH_2)_qOR^7$, $-NR^7C(O)R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-NR^7R^8$, $-OC(O)R^9$ or $OC(O)NR^7R^8$, and R^3 represents hydrogen or C_{1-4} alkyl;
or:
R^4 represents $-NHR^{10}$ and R^3 and $-NHR^{10}$ together form a 5- or 6- membered heterocyclic ring;

3. A compound of formula (I) according to either claim 1 or claim 2 wherein the group Ar^1 is selected from groups (a) and (b) as defined in claim 1.

4. A compound of formula (I) according to any of claims 1 to 3 wherein, in the group Ar^2, R^{11} is selected from hydrogen, C_{1-4}alkyl, hydroxy, halo, $-NR^{14}C(O)NR^{15}R^{16}$,

$-NR^{14}SO_2R^{15}$ and $XSO_2NR^{17}R^{18}$ wherein R^{14} to R^{18} are as defined in claim 1.

5. A compound of formula (I) according to any of claims 1 to 3 wherein, in the group Ar^2, R^{11} is selected from cyano, $-CONR^{15}R^{16}$, SR^{14}, SOR^{14} and SO_2R^{14}, wherein R^{14}, R^{15} and R^{16} are as defined in claim 1.

6. A compound of formula (I) according to any of claims 1 to 5 wherein R^{12} and R^{13} each represent hydrogen.

7. A compound of formula (I) according to any of claims 1 to 3 wherein R^{11} represents hydrogen and R^{12} and R^{13} each represent halogen or C_{1-6}alkyl.

8. A compund of formula (I) according to any of claims 1 to 7 wherein R^1 and R^2 are both hydrogen.

9. A compound of formula (I) according to any of claims 1 to 8 wherein each of m and n is independently 1 or 2, and p is zero or 1.

10. A compound of formula (I) selected from:

4-((1*R*)-2-{[2-((3*R*)-3-{[(2,6-Dichlorobenzyl)oxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

4-{(1*R*)-2-[(2-{(3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;

4-{(1*R*)-2-[(2-{(3*S*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;

2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{(3*R*)-3-[(pyridin-3-ylmethoxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]ethyl}phenol;

4-((1*R*)-2-{[2-((3*R*)-3-{[(6-Chloropyridin-3-yl)methoxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

4-((1R)-2-{[2-((3R)-3-{[(2,6-Dichloropyridin-3-yl)methoxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

4-{(1*R*)-2-[(2-{2-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol;

4-((1*R*)-2-{[2-((3*R*)-3-{[(5-Bromopyridin-3-yl)methoxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

3-[({(2*R*)-7-[2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]-2,3-dihydro-1,4-benzodioxin-2-yl}methoxy)methyl]benzonitrile;

3-[({(2*R*)-7-[2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]-2,3-dihydro-1,4-benzodioxin-2-yl}methoxy)methyl]benzamide;

4-[(1*R*)-2-({2-[(3*R*)-3-({[3-(Cyclopentylthio)benzyl]oxy}methyl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

4-[(1*R*)-2-({2-[(3*R*)-3-({[3-(Cyclopentylsulfonyl)benzyl]oxy}methyl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol;

2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{(3*R*)-3-[({5-[4-(methylsulfinyl)phenyl]pyridin-3-yl}methoxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]ethyl}phenol;

N-{3-[({(2*R*)-7-[2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]-2,3-dihydro-1,4-benzodioxin-2-yl}methoxy)methyl]phenyl}urea;

4-((1*R*)-2-{[2-((3*R*)-3-{[(4-Chlorobenzyl)oxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

4-((1*R*)-2-{[2-((3*R*)-3-{[(4-Fluorobenzyl)oxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

4-((1*R*)-2-{[2-((3*R*)-3-{[(3,5-Dimethylbenzyl)oxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{(3*R*)-3-[(1-phenylethoxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]ethyl}phenol;

2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({2-[(3*R*)-3-({[3-(methylsulfonyl)benzyl]oxy}methyl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl}amino)ethyl]phenol;

4-((1*R*)-2-{[2-((3*R*)-3-{[3-(2,6-Dichlorophenyl)propoxy]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

3-[({(2*R*)-7-[2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]-2,3-dihydro-1,4-benzodioxin-2-yl}methoxy)methyl]benzenesulfonamide;

6-{2-[(2-{(3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)pyridin-3-ol;

N-(5-{(1*R*)-2-[(2-{(3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-2-hydroxyphenyl)methanesulfonamide;

4-{(1*R*)-2-[(2-{(3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-2-fluorophenol;

4-{(1*R*)-2-[(2-{(3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-3-methylphenol;

(1*R*)-1-(4-Amino-3,5-dichlorophenyl)-2-[(2-{(3*R*)-3-[(benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]ethanol;

5-{(1*R*)-2-[(2-{(3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}ethyl)amino]-1-hydroxyethyl}-2-hydroxyphenylformamide;

or a salt, solvate or physiologically functional derivative thereof.

11. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) according to any of claims 1 to 10, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

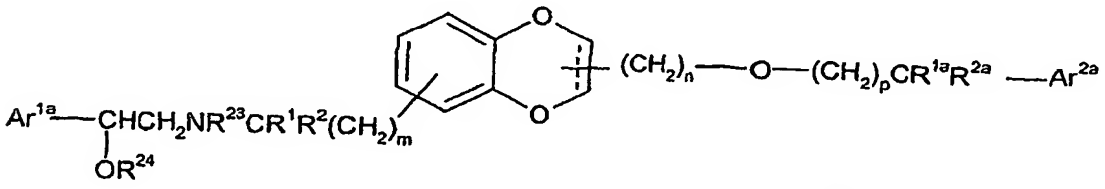
12. A compound of formula (I) according to any of claims 1 to 10, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

13. A pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 10, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

14. The use of a compound of formula (I) according to any of claims 1 to 10, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated.

15. A process for the preparation of a compound of formula (I), according to any of claims 1 to 10, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

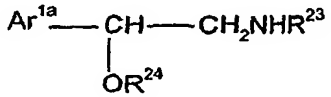
(a) deprotection of a protected intermediate, for example of formula (II).



(II)

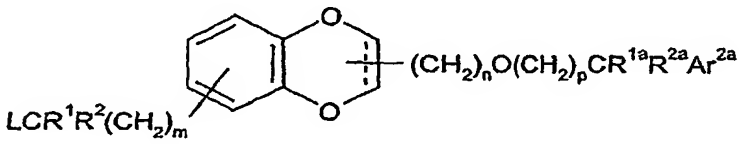
or a salt or solvate thereof, wherein R^1, R^2, R^{1a}, R^{2a}, m, n, p and ---- are as defined for the compound of formula (I), Ar^{1a} represents an optionally protected form of Ar^1; Ar^{2a} represents an optionally protected form of Ar^2 and R^{23} and R^{24} are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group;

(b) alkylation of an amine of formula



(VIII)

wherein Ar^{1a}, R^{23} and R^{24} are as defined for formula (II) with a compound of formula (XV):



(XV)

wherein ----, Ar^2, R^1, R^2, R^{1a}, R^{2a}, m, n and p are as defined for the compound of formula (II) and L is a leaving group as defined for formula (IX);

followed by the following steps in any order:

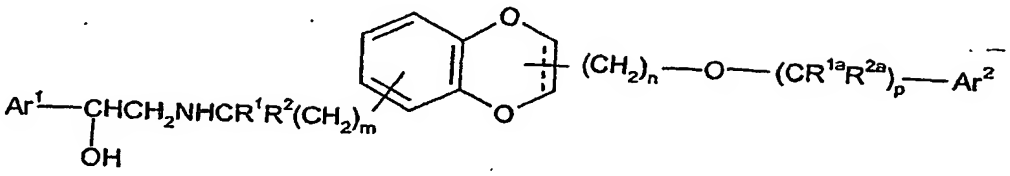
(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

ABSTRACT

The present invention relates to novel compounds of formula (I),



and salts, solvates and physiologically acceptable derivatives thereof, to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.